REMARKS

Claims 14, 16-21, 28, and 30-63 are canceled herewith. Applicant reserves the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Claims 1, 8, and 22 are amended herewith.

Independent claims 1, 8, and 22 are amended herewith to recite the formula for Formula I as requested by the Examiner.

Claim 1 is amended herewith to incorporate the limitation that the agent is "administered orally". Support for this limitation is found on page 15 lines 19-24 of the application as filed.

Claims 8 and 22 are also amended herewith to incorporate the limitation that the agent is "administered orally" in an amount "less than 1 mg/kg per day." Support for this limitation is found at least on page 10, line 4, and on page 15 lines 15-24 of the application as filed.

Claim 1 is amended herewith to delete reference to "or mature blood cells".

Claims 1 and 22 are amended herewith to specify that the target cells which are being stimulated are meamtopoietic cells "other than mature lymphocytes". Support for this limitation is found on page 8 of the application as filed.

Objection to the Abstract

The Abstract is amended herewith to comply with the recommendations of the Examiner to incorporate Formula I and to specifically mention ValBoroPro as an exemplary active agent.

Objection to the Drawings

The Examiner has objected to Figure 9 because the word "Hematopoesis" is mispelled in the heading. The correct spelling should be "Hematopoiesis".

Applicant presents replacement Figure 9 which includes the amended changes and one annotated sheet showing the changes. A Request for Approval of Proposed Drawing Corrections is enclosed along with revised Figure 9.

Objection to priority under 35 U.S.C. §119(e)

The Examiner notes that the Applicant has not complied with one or more conditions for receiving the benefit under 35 U.S.C. §119(e).

Applicant has amended the specification to include a specific reference to prior applications in the first sentence of the application. Applicant gratefully acknowledges the Examiner's finding that the instant claims are deemed to be entitled under 35 U.S.C. §119(e) to the benefit of the filing date of an earlier application.

Objection to informalities in the specification

The Examiner has objected to the following informality. At page 10, lines 4-6, the difference between 1mg/kg body weight and 0.1 mg/kg body weight/day is a factor of about 10, or one order of magnitude. The specification describes the difference as 10 orders of magnitude which is incorrect.

The appropriate correction was made by amending the specification to refer to the difference as "one order of magnitude".

No new matter has been added.

Objection to the claims

Claims 1-6, 8-12, 16-18, 22, 30, 34, 42, 52 and 58 are objected to for failure to recite Formula I in these claims.

Claims 1, 8, and 22 are amended herewith to explicitly recite Formula I in these independent claims.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

Double patenting rejection

Claims 16-18 are rejected under 35. U.S.C. §101 as claiming the same invention as that of claims 10-12 of prior US patent 6,300,314. Claims 16-18 are canceled.

Claims 1-6, 8-12, 16-18, 22, 30, 34, 42, 52 and 58 are rejected under the judicially created doctrine of obviousness-type double patenting rejection as being unpatentable over claims 1-36 of US patent 6,300,314. A terminal disclaimer in compliance with 37 CFR 1.321(c) is enclosed herewith to overcome the obviousness-type double patenting rejection.

Rejection of Claims 8, 9, and 34 under 35 U.S.C. §102(b):

Claims 34 was rejected under 35 U.S.C. §102(b) as being anticipated by Bachovchin et al. (US patent 5,462,928). Claim 34 is canceled.

Rejection of Claims 8, 9, and 34 under 35 U.S.C. §102(b):

Claims 8, 9, and 34 are rejected under 35 U.S.C. §102(b) as being anticipated by the WO Patent Application 94/03055 (PCT '055) According to the Examiner, PCT '055 teaches increasing hematopoietic activity and increasing T-cell production by administering DP-IV inhibitors such as ProBoroPro. The Examiner further characterizes this PCT application as teaching that administration of such inhibitors can be intravenous in a dosage of about 1-10 mg/kg/day or can be oral once or several times in a day at a dosage of 1-10 mg/kg/day. According to the Examiner, patients treated in accordance with PCT '055 include those undergoing chemotherapy or radiotherapy.

Claims 8 and 9 are directed to a method for shortening the time that a subject has an abnormally low level of hematopoietic or mature blood cells resulting from treatment with a hematopoietic cell inhibitor. Claim 34 is canceled.

Claim 8, as amended herewith, includes the limitation that the agent is administered orally in an effective amount that is less than 1 mg/kg/day. WO Patent Application 94/03055 (PCT '055) teaches "[a]dministration can be intravenously in a dosage of about 1-10 mg/kg or can be orally once or several times in a dosage of 1-10 mg/kg per day." PCT '055 does not teach oral administration of dosages of less than 1 mg/kg/day." Accordingly, the PCT '055 application does not anticipate claim 8 or 9.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 8 and 9 under 35 U.S.C. §102(b) as being anticipated by PCT '055.

Rejection of Claims 1-6, 8-12, 22, 42, 52 and 58 under 35 U.S.C. §103(a):

Claims 1-6, 8-12, 22, 42, 52 and 58 are rejected under 35 U.S.C. §103(a) as being obvious over the PCT '055. According to the Examiner, this rejection is an extension of the earlier rejection of claims as anticipated by this reference. The Examiner states that, it would be obvious to one of ordinary skill in the art to determine all operable and optimal administration schedules for the method of PCT '055 because administration schedules are routinely determined and optimized in

the pharmaceutical art. The Examiner acknowledges that the PCT '055 does not teach dosages of less than 1 mg/kg/day but concludes that it would have been obvious to one of ordinary skill in the art to determine all operable and optimal dosages for the method of PCT '055 because dosage is an art-recognized variable which is routinely determined and optimized in the pharmaceutical art. With respect to the differences between the PCT '055 dosage disclosure and that claimed by Applicant, the Examiner states:

> ". . . note that there is no indication in the WO patent application '055 that dosages less than 1 mg/kg/day will not work, that the intravenous dosage range disclosed by the WO patent application '055 overlaps Applicants' claimed dosage range because of the word 'about', and that the prior art claims directed to this method are not limited to any particular dosage. The difference between the prior art's exemplified dosage range and Applicants' claimed dosage range is minimal, and when the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference or range in the value is minor. See, Haynes International v. Jessup Steele Company, 28 USPQ2d 1652, 1655, n. 3 (Fed. Cir. 1993).

Applicant respectfully traverses this rejection for the following reasons.

Claims 42, 52, and 58 are canceled.

The remaining independent claims 1, 8, and 22 are amended herewith to include the limitation that the effective dose of active agent is administered orally at less than 1 mg/kg/day.

The dosage limitation which appears in the independent claims is neither taught nor suggested by the prior art. Indeed the prior art cited teaches away from the invention. The basis for Applicant's traversal of this rejection is set forth below.

The Examiner characterizes the differences between Applicant's claimed invention and that shown in the prior art as being a "minimal" difference in dosage range. The Examiner concludes that such a minimal difference is sufficient to support a prima facie finding of obviousness.

As acknowledged by the Examiner for the rejection of claims 8, 9 and 34 under 35 U.S.C. §102(b), PCT '055 does not teach a dosage less than about 1 mg/kg per day. PCT '055 teaches an intravenous dosage of about 1-10 mg/kg or alternatively an oral administration once or several times in a dosage of 1-10 mg/kg/day. The teachings of PCT '055 thus clearly suggest an oral dosage of much in excess of 1 mg/kg/day and not less than 1 mg/kg/day. If the lowest amount suggested for intraveneous treatment is 1mg/kg/day, then it would follow only that much more would be required for the blood levels and the same effect if administered orally. Hence PCT '055

explicitly suggests multiple oral doses per day. This would clearly suggest to one of ordinary skill in the art that if the minimum intravenous dose of 1mg/kg were to be match in an oral dosing schedule, then much more than 1 mg/kg/day would be required. This is a teaching away from the present invention than 1mg/kg/day. Based on the teachings of PCT '055, there is no motivation for one of ordinary skill in the art to use an oral dosage of less than 1 mg/kg/day and it would have been unexpected that such a low dose would be effective. Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success that oral dosages of less than 1 mg/kg/day (which are outside of the prescribed range in the PCT '055 reference) would be effective. Absent a motivation and absent an expectation of success, there is no basis for finding a *prima facie* case of obviousness of the invention as claimed.

Claims 2, and 4-7 that depend from independent claim 1, claims 9, 11-13, and 15 that depend from independent claim 8, and claim 27 that depends from independent claim 22, teach the administration of the agent of Formula I in an effective amount to restore levels of hematopoietic cell types (neutrophils, erythrocytes, or platelets) to a preselected normal or protective level.

PCT '055 does not suggest the administration of the agent of Formula I in an effective amount to restore particular levels of these particular hematopoietic cell types. Moreover, based on the teachings PCT '055, there is no motivation (let alone a reasonable expectation of success) for one of ordinary skill in the art to administer the agent in an effective amount to restore particular levels of these hematopoietic cell types. It is surprising that such levels as claimed can be restored using such low amounts of the claimed compounds.

Claim 3 that depends from independent claim 1, claim 10 that depends from independent claim 8, and claims 23-26 that depend from independent claim 22, teach the administration of the agent of Formula I in at least 2 doses in 18 hours periods. PCT '055 does not suggest the agent of Formula I in at least 2 doses in 18 hours periods. Moreover, based on the teachings PCT '055, there is no motivation for one of ordinary skill in the art to administer the agent of Formula I in at least 2 doses in 18 hours periods.

In view of the absence of a motivation and an expectation of success, Applicant respectfully requests the Examiner reconsider and withdraw the rejection of claims 1-6, 8-12, 22 under 35 U.S.C. §103(a) as being obvious over the PCT '055.

Rejection of Claims 52, 53, 58 and 59 Under 35 U.S.C. §103(a)

Claims 52 and 58 are rejected under 35 U.S.C. §103(a) as being obvious over the WO Patent Application 95/11689.

Claims 52 and 58 are cancelled herewith. Applicant reserves the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Rejection of Claims 1-3 and 22 under 35 U.S.C. §103(a):

Claims 1-3 and 22 are rejected under 35 U.S.C. §103(a) as being obvious over Huber et al. (US patent 6,040,145) According to the Examiner, Huber et al. teach stimulating proliferation of T-cells, especially $CD4^+$ and CTL's, both *in vivo* and *in vitro*, by administering very low concentrations, on the order of 10^{-8} to 10^{-12} M, of inhibitors of post-prolyl cleaving dipeptidase. The Examiner acknowledges that Huber et al. do not teach Applicant's claimed dosages but that the inhibitor concentrations desired by Huber et al. are consistent with those disclosed by Applicant. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimum blood concentrations and inhibitor concentrations.

Claim 1 is amended herewith to delete reference to "or mature blood cells."

Claim 1 and 22 are amended herewith to specify that the target cells which are being stimulated are hematopoietic cells other than mature lymphocytes.

Claim 1 as amended and the claims dependent thereon (Claims 2 and 3) are directed to a method for treating a subject to stimulate hematopoiesis in a subject. The method involves administering to the subject an amount of an agent of Formula I that is effective to increase the number of hematopoietic cells other than mature lymphocytes in the subject.

Claim 22 as amended is directed to a method for treating a subject to increase the number of hematopoietic cells other than mature lymphocytes in the subject. The method involves administering to the subject an amount of an agent of Formula I that is effective to increase the number of hematopoietic cells other than mature lymphocytes in the subject.

Thus, each of Claims 1-3 and 22 are directed to stimulating hematopoiesis to increase the number of hematopoietic cells other than mature lymphocytes in the subject.

In contrast to the invention as claimed, Huber et al. teach stimulating the proliferation of mature lymphocytes. $CD4^+$ and CTL's ($CD8^+$) and all other lymphocytes are mature, differentiated

cells. Thus, Huber et al. targets the proliferation of cells which are distinct in phenotype and activity from the hematopoietic cells targeted in the pending claims.

In contrast to Huber et al., the claimed invention is based upon a number of surprising and unexpected findings as they relate to the stimulation of hematopoietic cells, particularly, primitive hematopoietic progenitor cells (page 2, line 10-25).

> "The invention is based upon a variety of surprising and unexpected findings. It has been discovered, unexpectedly, that the agents useful according to the invention stimulate growth factor production by stromal cells. It also has been discovered, unexpectedly, that the agents useful according to the invention stimulate proliferation of primitive hematopoietic progenitor cells, but do not stimulate directly the differentiation or proliferation of committed progenitor cells. It further has been discovered, unexpectedly, that the agents useful according to the invention can be administered at doses much lower than would have been expected according to the teachings of the prior art. Another unexpected finding is that the agents according to the invention can accelerate the time it takes to achieve hematopoietic cell recovery after treatment with an hematopoietic cell inhibitor. Another unexpected finding is that the agents useful according to the invention can at relatively low doses, restore normal levels of neutrophils at least as fast as the most successful commercially available product used worldwide for this purpose, except that the agents useful according to the invention can be used orally, whereas the commercially available product (which represents more than a billion dollar market) must be injected. These unexpected results have important therapeutic and experimental research implications."

The teachings of Huber et al. that DPIV inhibitors are useful for stimulating proliferation of T-cells would not be considered by one of ordinary skill in the art as predictive of the ability of such inhibitors to stimulate other cell types, particularly immature cell types at least because such progenitor cells of neutrophils, erythrocytes, and platelets *reside in the bone marrow*. In contrast, the Huber mature lymphocytes reside in the peripheral circulation which is a different anatomical location. Thus, it would not have been obvious to one of ordinary skill in the art that the particular concentrations of DPIV inhibitors that are useful for stimulating the proliferation of T-cells in, for example, peripheral blood, would be useful for (1) stimulating cells which are distinct in phenotype; and (2) cells which are located in the bone marrow.

Moreover, $CD4^+$ and $CD8^+$ and other lymphocytes are mature cells which are distinct in lineage and function from neutrophils, erythrocytes, and other leukocytes. Accordingly, the teachings of Huber et al. that DPIV inhibitors are useful for stimulating proliferation of T-cells (by their nature, mature cells), would be useful for stimulating proliferation of different cell types at low concentrations. The above quoted paragraph from the Summary of the Invention describes the

unexpected nature of the results that are reported in the pending application. Thus, even if one of ordinary skill in the art were motivated to attempt to stimulate hematopoietic cells in view of Huber et al. (which Applicant disagrees with), there is no reasonable expectation of success that the low concentrations of DPIV inhibitor would be useful for this purpose -- particularly in view of Applicant's teachings in the Summary of the Invention of the unexpected and surprising results which form in part, the basis for the pending application.

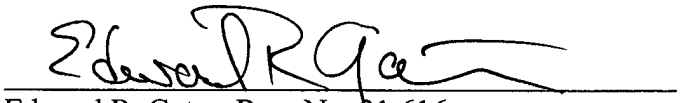
In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-3 and 22 under 35 U.S.C. §103(a) as being obvious over Huber et al.

Summary

Applicant believes that each of the pending claims now is in condition for allowance. Applicant respectfully requests that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicant's attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 232).

Respectfully Submitted,



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